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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,130	05/14/2001	Keith H.S. Campbell	105434.105001	8898

7590 04/16/2007

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/600,130	CAMPBELL, KEITH H.S.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-47,49,50,56-63,66-76,83-88 and 90-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-47,49,50,56-58,66-76,83-88 and 90-92* is/are rejected.

7)☒ Claim(s) *59-63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner for the instant application is now Valarie Bertoglio, AU1632.

Applicant's reply dated 09/13/2005 was received 07/28/2006 along with a petition to withdraw abandonment. This petition was not granted but the subsequent petition, 11/28/2006 was granted. Thus, prosecution is hereby reopened and Applicant's reply received 07/28/2006 is currently under consideration.

Claims 1-41,48,51-55,64-65,77-82,89 and 93-113 have been cancelled. Claims 42-47,49-50,56-63,66-76,83-88 and 90-92 are pending and under consideration in the instant office action.

Claim Objections

Claims 59-63 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 69 is objected to because of the following informalities: Claim 69 reads "animal a fetus" at step (b) and step (c) rather than "animal fetus". This appears to be a typographical error. Appropriate correction is required.

Claim 57 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Double Patenting

The objection to claims 89 and 93-113 under 37 CFR 1.75 as being substantial duplicates of other pending claims is rendered moot by the cancellation of claims 89 and 93-113.

Applicant is advised that should claim 88 be found allowable, claim 91 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 42-47,49-50,56-58,66-76,83-87 and 90-92 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reconstituting a non-primate mammal practicing steps (i)-(iv), does not reasonably provide enablement for use of the claimed method with any animal, including primate species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The

rejection is maintained for reasons of record set forth at pages 4-6 of the office action dated 04/13/2005.

The rejection is withdrawn as it relates to claims 59-63,88 and 90-92 as these claims are limited to non-primate species.

Applicant's arguments have been fully considered and are not persuasive.

Applicant notes that reconstituted embryos can have uses other than producing an animal, including production of ES cells or other cell types (see paragraph bridging paged 6-7 of Applicant's remarks received 07/28/2006). Applicant argues that Hwang *et al.* (2004) reported the derivation of a pluripotent ES cell line from a cloned human blastocyst via somatic cell nuclear transfer. Applicant says primate embryos and primate pluripotent mammalian cells derived therefrom have been produced via nuclear transfer.

In response, Applicant's arguments are not persuasive with respect to cloned primate embryos. As noted by both Simerly [**Science**, 300:297, 2003] and by Vogel [**Science**, 300:225-227, 2003], primate cloning had not been attainable using somatic cells because cells fail to undergo proper cell division. Vogel states that a few cell divisions occur before the developmental program is "hopelessly derailed" (paragraph bridging columns 1-2, page 225). Proteins necessary for proper cell division are removed upon removal of the oocyte nucleus in primates, but not other mammals, as these proteins are not localized with the chromosomes in non-primate mammals (page 225, col. 2, paragraph 2). Furthermore, with respect to the teachings of Hwang 2004), this paper was retracted by *Science* magazine as containing fabricated data (see **Science,** 311:335, 2006). Thus, the art, well after the date of filing of the instant application, teaches that even the earliest events in cloning a primate from a somatic cell are hindered and the

mechanisms underlying this were not fully understood such that one could make a primate nuclear transfer embryo even to early blastocyst stages having cells competent to form a cell line.

Applicant also argues that Lanza *et al.* support that, in terms of cloning efficiencies of other mammalian species, Simerly *et al* (2003) failed to attempt enough nuclear transfers to deem it "unachievable". In response, while the efficiency of cloning in any species is very low and that a very large number attempts must be made to meet success, this fact fails to overcome the findings in the art that primate cells fail to undergo proper cell division following somatic cell nuclear transfer. The teachings of Simerly (2003) and Vogel (2003) support an underdeveloped nature and very high degree of unpredictability in the art of cloning primates at the time the instant application was filed. The failure to clone a primate even to early embryonic stages does not appear to be a matter of inefficiency but to a difference in oocyte morphology and cell division that requires undue experimentation to characterize and overcome. While it is agreed that this does not render primate cloning "unachievable" for the future, it clearly supports the unpredictability of success and lack of guidance in the art, as well as the specification, at the time the application was filed.

It is noted that Applicant's arguments are not relevant to claims 45,46 and 69-76 as they require development of an embryo to term.

It is also noted that the claims are broadly drawn to any species of animal, including non-mammals such as birds, fish, and insects. The art of somatic cell transfer as referred to in the specification, relates to mammalian species. Cloning by somatic cell nuclear transfer has not

been developed as broadly encompassed by the claims and is not supported by the specification. Therefore, the instant claims should be limited to non-primate mammals, rather than, animals.

New Matter

The rejection of claims 89 and 93-113 as introducing new matter into the specification is rendered moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57 and 71-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 is unclear because it is required that the first oocyte of claim 42 be enucleated. However, step ii if claim 42requires removal of the nucleus from the oocyte. Thus, the relationship between claim 57 and 42 is not clear.

The terminology "further manipulated" in claims 71 and 72 is unclear. It is not known what kind of manipulation is being referred to or what is intended to be encompassed by the claims. It is also unclear in claim 71, whether the phrase "prior to full development of the embryo" means development to the last embryonic stage just prior to becoming a fetus or whether it is referring to full development into a born offspring. Likewise, claim 72 is further unclear because it is not clear whether the phrase "prior to full development of the fetus" means

development to the last fetal stage just prior to becoming a live-born offspring or whether it is referring to full development into a born offspring.

Claims 73 and 74 are unclear. The claims refer the method of claim 69, wherein a cell line is derived from the embryo or fetus of the claims. It is not clear if the claims encompass preparing the animal of claim 69 (see preamble of claim 69 and step c), if at steps (a) or (b), the embryo or fetus is used to make a cell line.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Valarie Bertoglio
Examiner
Art Unit 1632

Notice of References Cited	Application/Control No. 09/600,130	Applicant(s)/Patent Under Reexamination CAMPBELL, KEITH H.S.	
	Examiner Valarie Bertoglio	Art Unit 1632	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

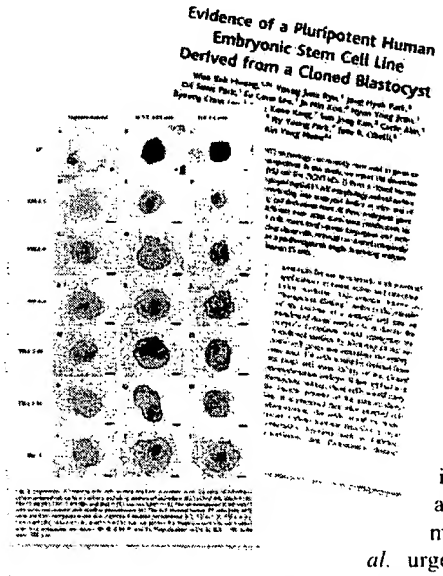
*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Simerly, C et al., Molecular correlates of primate nuclear transfer failures, Science, 300:297, 2003.
	V	Vogel, G, 2003, Misguided chromosomes foil primate cloning, Science, 300:225 and 227.
	W	Kennedy, D. 2006, Editorial Retraction, Science, 311:335.
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

LETTERS

edited by Etta Kavanagh

Editorial Retraction



THE FINAL REPORT FROM THE INVESTIGATION COMMITTEE of Seoul National University (SNU) (*1*) has concluded that the authors of two papers published in *Science* (*2*, *3*) have engaged in research misconduct and that the papers contain fabricated data. With regard to Hwang *et al.*, 2004 (*2*), the Investigation Committee reported that the data showing that DNA from human embryonic stem cell line NT-1 is identical to that of the donor are invalid because they are the result of fabrication, as is the evidence that NT-1 is a bona fide stem cell line. Further, the committee found that the claim in Hwang *et al.*, 2005 (*3*) that 11 patient-specific embryonic stem cells line were derived from cloned blastocysts is based on fabricated data. According to the report of the Investigation Committee, the laboratory "does not possess patient-specific stem cell lines or any scientific basis for claiming to have created one." Because the final report of the SNU investigation indicated that a significant amount of the data presented in both papers is fabricated, the editors of *Science* feel that an immediate and unconditional retraction of both papers is needed. We therefore retract these two papers and advise the scientific community that the results reported in them are deemed to be invalid.

As we post this retraction, seven of the 15 authors of Hwang *et al.*, 2004 (*2*) have agreed to retract their paper. All of the authors of Hwang *et al.*, 2005 (*3*) have agreed to retract their paper.

Science regrets the time that the peer reviewers and others spent evaluating these papers as well as the time and resources that the scientific community may have spent trying to replicate these results.

DONALD KENNEDY
Editor-in-Chief

References

1. Investigation Committee Report, Seoul National University, 10 Jan. 2006. (Members: Chairman Myung-Hee Chung, SNU, Uhtaek Oh, SNU, Hong-Hee Kim, SNU, Un Jong Pak, SNU, Yong Sung Lee, Hanyang University, In Won Lee, SNU, In Kwon Chung, Yonsei University, Jin Ho Chung, SNU)
2. W. S. Hwang *et al.*, Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst, *Science* **303**, 1669 (2004).
3. W. S. Hwang *et al.*, Patient-Specific Embryonic Stem Cells Derived from Human SCNT Blastocysts, *Science* **308**, 1777 (2005).

Madison and Climate Change Policy

IN THEIR POLICY FORUM "A MADISONIAN APproach to climate policy" (16 Sept. 2005, p. 1820), D. G. Victor *et al.* oppose international cap and trade agreements with binding greenhouse gas emissions limitations. They argue for bottom-up local policy experiments as the best way to promote action and eventually lead to wider cooperation to address climate change. They claim that this approach (as contrasted with top-down rules) is what Madison envisioned in *The Federalist Papers*—the laboratory of multiple states in federalism. Yet Victor *et al.* have mistaken and misappropriated Madison and advocated a policy that will not solve the global tragedy of the climate commons.

Victor *et al.* neglect that Madisonian federalism involved a strong central government with significant coercive power. Madison was advocating not pure bottom-up diversity, but a new Constitution replacing the Articles of Confederation with an overarching legal and institutional framework to govern and mobilize both the states and the private sector in the common interest.

Victor *et al.* also mischaracterize the plurilateral treaty approach advocated by Stewart and Wiener (*1*). This approach involves building agreements among plural coalitions of willing nations to create parallel systems of international emissions trading. It would not be a "top-down" system, nor would it approach the degree of centralization involved in Madison's version of federalism. It would avoid the difficulties of establishing a single universal cap and trading system under the Kyoto Protocol and focus on cooperation among the major emitting countries, as Victor *et al.* urge. The plurilateral cap and trade approach would foster a variety of trading systems to encourage precisely the diversity and experimentation in policy and practice that Victor *et al.* favor. But it would also involve binding mutual commitments by participants.

In contrast to both Madisonian federalism and plurilateral trading, Victor *et al.* argue for bottom-up local policies that they hope will somehow help move states from uncoordinated autarchy to the accretion of shared norms and informal cooperation. In certain situations under favorable conditions—generally involving small, close-knit groups—some tragedies of the commons can be successfully addressed through such informal development of shared norms (*2*). But often, especially at larger scales where reciprocity and monitoring are more elusive, the tragedies persist unless stronger institutions provide incentives for action in the common good [e.g., (*3*–*5*)]. Between bottom-up diversity and top-down rule, plurilateral cap and trade systems would provide these incentives while avoiding excessive centralization.

Effective climate policy will require emissions abatement by China, India, and other major developing countries, as well as by the United States and Europe, but purely bottom-up experiments have little chance of engaging all of these countries anytime soon. Some

virus in cell culture and plans to slog through *all* drugs currently approved for *any* condition by the Food and Drug Administration, says Army virologist Peter Jahrling. If an approved drug works against SARS, it could be available much faster than a new one. CDC and other labs are comparing the virus's genome sequence to those of other coronaviruses—which can infect a range of avian and mammalian species—to determine its likely origin.

For network scientists, Stöhr has tried to orchestrate the fair distribution of a key commodity: scientific credit. He initially proposed that they submit three papers to *NEJM*: one produced by three groups in Hong Kong, one co-authored by German researchers and CDC, and one by groups that found the metapneumovirus. That plan fell apart when CDC, which had been invited by *NEJM* to write a paper, decided it preferred to go it alone. Fortunately, *NEJM* editors said they would consider publishing all four. Drosten has teamed with colleagues across Germany as well as Osterhaus and a group from the Pasteur Institute in Paris to describe the methods they used to track the coronavirus. "It appears there's enough flesh on the bones for everybody," says Osterhaus.

Meanwhile, Stöhr is also compiling a paper for *The Lancet* chronicling the current collaboration. He concedes to being slightly taken aback last week when, after each lab had submitted 250 words about its own role, Gerberding stole some of the network's thunder in an *NEJM* editorial that was posted online 2 April. But his hope is that the example set by the SARS network will long outlast any debate over who came first.

–MARTIN ENSERINK AND GRETCHEN VOGEL

NUCLEAR TRANSFER

Misguided Chromosomes Foil Primate Cloning

While governments around the world debate how to prevent human reproductive cloning, it seems that nature has put a few hurdles of its own in the way. On page 297, a team reports that in rhesus monkeys, cloning robs an embryo of key proteins that allow a cell to divvy up chromosomes and divide properly. Unpublished data from this and other groups suggest that the same problem may also thwart attempts to clone humans.

There are potential ways around the newfound obstacle, but for now, groups that made controversial claims that they would use the techniques that produced Dolly the sheep to create human babies are unlikely to succeed.

It is almost as if someone "drew a sharp line between old-world primates—including people—and other animals, saying, 'I'll let you clone cattle, mice, sheep, even rabbits and cats, but monkeys and humans require something more,' " says Gerald Schatten of the University of Pittsburgh School of Medicine, a leader of the rhesus monkey study.

Schatten and his colleagues have tried hundreds of times to clone monkeys, only to fail. Indeed, although several groups have attempted it, no one has yet produced a monkey through somatic cell nuclear transfer, the process by which a nucleus from one cell is extracted and injected into an egg whose own nucleus has been removed. "The failure to clone any primate has so far been startling," says Rudolf Jaenisch of the Massachusetts Institute of Technology in Cambridge, who studies cloning in mice.

The scientists had suspected for several years that something was disturbing cell division in cloned embryos. The embryos seemed normal at their earliest stages, but none developed into a pregnancy when implanted. When the researchers looked more closely, they realized why: Many of the cells in a given embryo had the wrong number of chromosomes. Some had just a few, whereas others had twice as many as they should. Although embryos can survive for a few cell divisions with such defects, soon the developmental program becomes hopelessly derailed.

To find out what was interfering with proper cell division, the team fluorescently labeled the cell-division machinery. The cells' mitotic spindles, which guide chromosomes to the right place during cell division, were completely disorganized. And two proteins that help organize the spindles, called NuMA and HSET, were missing.

A look at unfertilized rhesus oocytes explained why. The team found that the spindle proteins are concentrated near the chromosomes of unfertilized egg cells—the same chromosomes that are removed during the first step of nuclear transfer. In most other mammals, Schatten says, the proteins are scattered throughout the egg, and removing the egg's chromosomes seems to leave enough of the key proteins behind for cell division to proceed.

The work "explains why no one has yet succeed in achieving normally developing embryos from human nuclear transfer," says Roger Pedersen of the University of Cambridge, U.K., who attempted human nuclear transfer experiments at his previous laboratory at the University of California, San Francisco. "Primate eggs are biologically different." Schatten says preliminary data suggest the proteins are also concentrated near the nuclear material in unfertilized human eggs.

A cloning lab might surmount the hurdle, says Schatten, by reversing the order of the traditional nuclear transfer procedure: First add an extra nucleus, then activate cell division, and finally remove the egg's DNA. The find "will make people think differently about the optimum sequence of nuclear transfer procedures," says Ian Wilmut of the Roslin Institute in Midlothian, Scotland, a leader of the team that cloned Dolly.

Even if scientists could overcome the obstacles, however, another study suggests that ▶

Missing in action. In human embryos, as in this egg fertilized by two sperm (red lines), proteins from egg and sperm combine (yellow) to guide cell division. Embryos formed by nuclear transfer lack these proteins.

CREDIT: G. SCHATTEN/UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE

further developmental problems threaten clones of all species. Jaenisch and his colleagues report in the 15 April issue of *Development* that genes important to early development frequently fail to turn on in mouse embryos cloned from adult cells. That failure helps explain the low survival rate of such embryos, Jaenisch says. But he notes that the team's work—which examined the expression of just 11 genes—is only the tip of the iceberg. In other experiments, the researchers have found that even apparently healthy cloned mice show abnormal levels of gene expression. "There may be no normal clones," Jaenisch says.

Although revising the nuclear transfer procedure might help solve the cell-division problem, it is harder to imagine a solution for the faulty gene regulation that Jaenisch and his colleagues see. "We're looking at a more fundamental problem," he says.

The biological roadblocks would seem to be good news for those worried about the ethical implications of human cloning, says Schatten. "This reinforces the fact that the charlatans who claim to have cloned humans have never understood enough cell or developmental biology" to succeed, he says. The debate will go on, but nature already seems to have imposed its own limits on cloning.

–GRETCHEN VOGEL

GENE EVOLUTION

Cannibalism and Prion Disease May Have Been Rampant in Ancient Humans

Some call it the laughing disease; others, kuru. This neurodegenerative disorder is universally fatal and 40 years ago killed almost 10% of a small New Guinea tribe called the Fore. Now molecular biologists propose that similar epidemics plagued prehistoric humans. Both then and more recently, kuru, a prion disease, was transmitted through cannibalism, Simon Mead and John Collinge of University College London and their colleagues claim in a report online in *Science* this week (www.sciencemag.org/cgi/content/abstract/1083320). They base their conclusions on the worldwide distribution of variants of the prion gene.

The work lends support to the idea that ancient people once regularly munched on their peers. This conclusion will be controversial, says John Hardy, a geneticist at the National Institute on Aging in Bethesda, Maryland. Nonetheless, "I think [Collinge and colleagues] might be right."

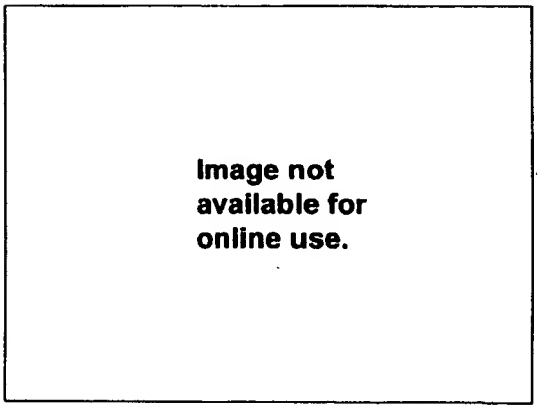
Until 50 years ago, the Fore reportedly had a tradition of eating the dead. In the 1960s, Carleton Gajdusek of the National Institute of Neurological Diseases and Stroke in Bethesda demonstrated that kuru was an infectious disease: Once cannibalism was banned, kuru disappeared.

Gajdusek blamed a slow-growing virus for the disease, but now the prime suspect in kuru is a malformed miniature protein called a prion. Contorted prions cause other, native prions to misfold, clump together, and kill brain cells. A similar process is believed to cause Creutzfeldt-Jakob disease (CJD) in humans and scrapie in sheep. Although some prion diseases occur spontaneously, in many cases, humans or other animals contract them by eating infected tissue.

A decade ago, Collinge showed that people carrying two identical copies of the gene for the prion protein are more susceptible to developing CJD than people who carry two unmatched gene variants. Although the variants create proteins that differ by only one amino acid, the mismatch somehow protects people against the disease.

To understand the history of the prion gene, Collinge's team looked at DNA from the Fore and also from 1000 people representing other groups around the world. All ethnic groups examined carried two versions of the prion gene.

The variants' widespread existence suggests that they have been conserved throughout human history, the team claims. Based on additional comparisons across cultures and with chimp DNA, the ▶



CREDITS: (TOP TO BOTTOM) P. BAGLA/WHO

Deadly epidemic. Prehistoric people may have succumbed to the prion disease that killed this man from a New Guinea tribe.

ScienceScope

India, WHO Attack Polio

NEW DELHI—Calling India "the number one priority for stopping the transmission of polio," WHO Director-General Gro Harlem Brundtland this week traveled to the north Indian state of Uttar Pradesh to launch a final assault on the disease. With 55 new cases already this year, Brundtland says that "Uttar Pradesh is the epicenter" of a global battle to eradicate polio by 2005.

India joins Nigeria, Egypt, Pakistan, Afghanistan, Niger, and Somalia as the only countries with indigenous wild polio, and last year it was home to five of every six new cases. Uttar Pradesh was also the source of outbreaks in two other Indian provinces, and this winter a Lebanese youth who never left his village was paralyzed by a virus traced back to India.

WHO officials say the latest epidemic is the result of fewer vaccination campaigns than planned and a failure to achieve blanket coverage during home visits. This year officials hope to reach every child under 5 in six campaigns. Although Brundtland says that "we have the tools and the strategies to finish this job," WHO remains $275 million short of what it estimates is needed to eradicate the disease.

–PALLAVA BAGLA

Fast Flux, R.I.P.

PORTLAND, OREGON—After displaying more lives than a cat, the Fast Flux Test Facility, a nuclear research reactor in Hanford, Washington, has finally run out of luck. A federal appeals court in San Francisco last week denied a local group's bid to keep the Department of Energy reactor on standby for possible conversion to a for-profit producer of medical radioactive isotopes.

The research reactor went online in 1980 but was shut down just 12 years later because of high operating costs. The government has since spent about $35 million a year to keep the reactor idle while searching for possible new missions, such as producing tritium for nuclear weapons and radioisotopes for spacecraft batteries. Those hopes came to an end this week, as workers began draining molten sodium coolant from the reactor's core. Once drained, the reactor "would be extremely hard to restart," says Michael Turner of Fluor Hanford, the company doing the work. The shutdown could take 10 years and cost more than $600 million.

–ROBERT F. SERVICE

Molecular Correlates of Primate Nuclear Transfer Failures

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Somatic cell nuclear transfer (SCNT) (*1*) in nonhuman primates could accelerate medical research by contributing identical animals for research and clarifying embryonic stem cell potentials (*2*). Although rhesus embryos begin development after embryonic cell nuclear transfer (ECNT) (*3–5*), there has only been one report of rhesus births after ECNT (*3*), and that report has not been replicated.

Here, molecular obstacles were identified using 716 rhesus oocytes in four experimental studies: set A, SCNT [rhesus cumulus, umbilical cord blood, epithelial-derived fibroblasts, and inner cell mass–derived precursor embryonic stem cells; 193 oocytes; 62.8% nuclear transfer (NT) success assayed by interphase nucleus formation], and set B, ECNT from dissociated 16- to 32-cell stage embryos (381 oocytes; 97.2% NT success), because ECNT success is greater than SCNT (*1*). Because meiotic spindle removal appeared to be responsible for these NT failures, we performed two additional experiments in which either we did not remove the spindle (set C) or we removed and reinserted it (set D). In set C, NTs into concurrently fertilized oocytes generated tetraploids (55 oocytes; 54.4% success), whereas in set D, fertilization of reconstituted oocytes (that had previously been enucleated and then renucleated) generated diploids (95 oocytes; 67.1% success).

Rhesus NTs (*6*) look superficially normal, yet no pregnancies resulted from 33 embryos transferred into 16 surrogates (compared with seasonably variable 28 to 66% pregnancy rates by assisted reproduction) (*7*). DNA and microtubule imaging showed disarrayed mitotic spindles with misaligned chromosomes (Fig. 1A; all 116 ECNTs and all 30 SCNTs examined displayed aberrant spindles). Despite these defects, cleavages continue, but unequal chromosome segregations produce aneuploid embryos.

NuMA (Nuclear-Mitotic Apparatus), a matrix protein responsible for spindle pole assembly (*8*), concentrates at centrosomes in unfertilized meiotic (Fig. 1B) and fertilized mitotic cells (Fig. 1C). After NT, NuMA is not detected on the abnormal mitotic spindles (Fig. 1D) or in enucleated oocytes. HSET and Eg5 are mitotic kinesin motors (*8*, *9*). HSET, found during meiosis and mitosis, is not detected in NT spindles (Fig. 1E). Eg5 detects centromere pairs at meiosis and mitosis, including misaligned ones on NT spindles (Fig. 1F). Thus, meiotic spindle removal depletes the ooplasm of NuMA and HSET, both vital for mitotic spindle pole formation.

Normal spindles found in tetraploids suggest meiotic spindle removal as the source of NT anomalies. In tetraploids, chromosomes aligned properly on bipolar spindles with centrosomal NuMA (Fig. 1G). NT mitotic spindles could be distinguished from the fertilized spindle by the sperm tail. Similarly, fertilization of reconstituted oocytes resulted in apparently normal divisions. Thus, manipulation of the embryos alone was not the cause of the problem, and proper mitotic spindles can be organized around somatic chromosomes if the meiotic spindle is left intact.

Primate NT appears to be challenged by stricter molecular requirements for mitotic spindle assembly than in other mammals. In cattle, the somatic centrosome is transferred during NT (*10*), whereas mice rely on the oocyte's maternal centrosome (*11*). Also, NuMA and HSET are not exclusively concentrated on the meiotic spindle in mammals other than primates (*8*). With current approaches, NT to produce embryonic stem cells in nonhuman primates may prove difficult—and reproductive cloning unachievable.

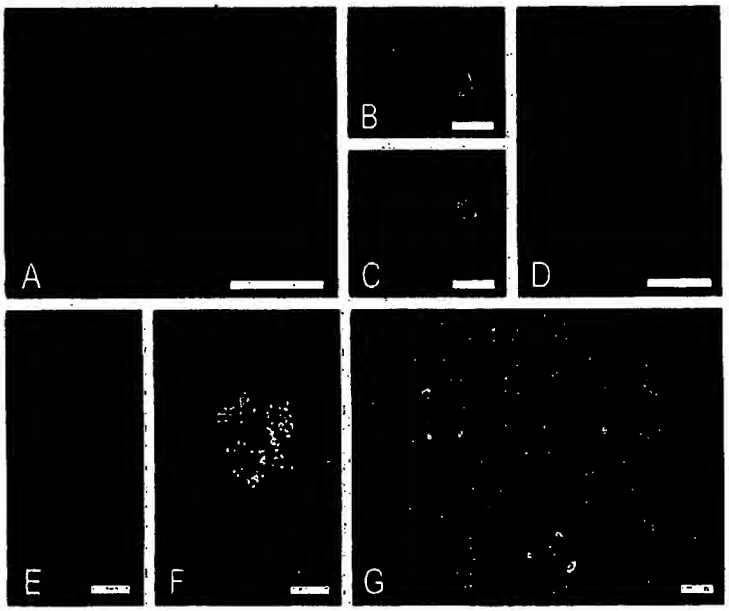

Fig. 1. Faulty mitotic spindles produce aneuploid embryos after primate nuclear transfer. (A) Defective NT mitotic spindle with misaligned chromosomes. Centrosomal NuMA at meiosis (B) and mitosis (C), but not in mitotic spindles after NT (D). The centrosomal kinesin HSET is also missing after NT (E), but not centromeric Eg5. (F). Bipolar mitotic spindles with aligned chromosomes and centrosomal NuMA after NT into fertilized eggs (G). DNA, microtubule, NuMA, and kinesin imaging as in (*7*, *8*). Blue, DNA; red, β-tubulin; green, NuMA in (B), (C), (D), and (G); HSET in (E); and Eg5 in (F). Scale bar, 10 μm.

References and Notes

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